Ossifying Fibroma Tumor Stem Cells Are Maintained by Epigenetic Regulation of a TSP1/TGF-beta/SMAD3 Autocrine Loop.

Journal: Cell Stem Cell

Publication Year: 2013

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PubMed link: 24209761

Funding Grants: Oral and Craniofacial Reconstruction Using Mesenchymal Stem Cells, CIRM Stem Cell Biology Training Program

Public Summary:
In conclusion, our work establishes a human stem-cell-based benign OF tumor model with a functional phenotype regulated by JHDM1D/TSP1/TGF-β/SMAD3 autocrine-mediated hyperactive TGF-β signaling. Blockage of TGF-β signaling and its autocrine components in OFMSCs can rescue osteogenic deficiency and suppress stromal growth, therefore providing a unique therapy for OF lesions.

Scientific Abstract:
Abnormal stem cell function makes a known contribution to many malignant tumors, but the role of stem cells in benign tumors is not well understood. Here, we show that ossifying fibroma (OF) contains a stem cell population that resembles mesenchymal stem cells (OFMSCs) and is capable of generating OF-like tumor xenografts. Mechanistically, OFMSCs show enhanced TGF-beta signaling that induces aberrant proliferation and deficient osteogenesis via Notch and BMP signaling pathways, respectively. The elevated TGF-beta activity is tightly regulated by JHDM1D-mediated epigenetic regulation of thrombospondin-1 (TSP1), forming a JHDM1D/TSP1/TGF-beta/SMAD3 autocrine loop. Inhibition of TGF-beta signaling in OFMSCs can rescue their abnormal osteogenic differentiation and elevated proliferation rate. Furthermore, chronic activation of TGF-beta can convert normal MSCs into OF-like MSCs via establishment of this JHDM1D/TSP1/TGF-beta/SMAD3 autocrine loop. These results reveal that epigenetic regulation of TGF-beta signaling in MSCs governs the benign tumor phenotype in OF and highlight TGF-beta signaling as a candidate therapeutic target.